Specialty Conference

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Kidney Stones

The prevalence of kidney stones has steadily risen during this century; passage of a calculus and a positive family history increase the probability of recurrence. Findings from recent studies on the cause of renal calculi have stressed crystallization and crystal aggregation of stone minerals from supersaturated urine, rather than excessive organic matrix. Absence of normal urine inhibitors of calcium salts is also stressed. Formation of calcium oxalate stones is the major problem. Therapy with decreased calcium and oxalate intake, thiazides, phosphate salts and allopurinol in various combinations has substantially decreased the prevalence of recurrent stones. The rationale for the use of allopurinol is that uric acid salts enhance the tendency for calcium oxalate to crystallize from supersaturated urine. The hypercalciuria seen in 30 percent to 40 percent of patients with oxalate stones is usually caused by intestinal hyperabsorption of calcium. Although patients with uric acid calculi constitute only a small fraction of those in whom stones form, they represent a group in whom good medical therapy, based on sound physiologic principles, has proved extremely successful. Renal tubular syndromes lead to nephrocalcinosis and lithiasis through hypercalciuria, alkaline urine and hypocitraturia, the latter an inhibitor of calcium salt precipitation. Recent advances in surgical techniques are discussed, including the rationale for removing staghorn calculi. The ileal ureter and coagulum pyelolithotomy deserve special emphasis.

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CHARLES R. KLEEMAN, MD:* During this century there has been a steady rise in the prevalence of upper urinary tract stones[1]; however, the precise incidence in any but the smallest communities has never been determined.[2] A recent study (which may have general applicability) by Ljunghall and Hedstrand[3] is a retrospective analysis of the natural history of upper urinary tract stones in ambulatory middle-aged men in an urban population (Uppsala, Sweden). The incidence of stones in 2,322 men was 13.7 percent. This figure was based on four criteria: (1) spontaneous passage of a stone noted by the patient, (2) operative removal of a stone, (3) a stone or stones of the upper urinary tract shown on x-ray films and (4) characteristic clinical findings judged by a physician at the time of the symptoms.

Despite the availability of excellent hospital facilities in the community, only 23 percent of these men had on any occasion been admitted to hospital. Hospital statistics, therefore, cannot be relied on for determining the prevalence of nephrolithiasis. Ljunghall and Hedstrand[3] presented incidence statistics available in the literature from other Scandinavian countries, the United States and Great Britain: the incidence varied from 3.5 percent to 13.7 percent, with an average of 7 percent. In the population they studied, they noted a progressive increase in the total number of patients with kidney stones during each five-year period, beginning with those less than 19 years old to those 50 years old. In about 42 percent of patients there had been at least one recurrence of stones by age 50; the risk of relapse increased progressively after five years from 31.5 percent to 72 percent in patients who had their first stone attack more than 20 years previously. Therefore, formation of kidney stones is not a singular event but a process in which the risk of recurrence remains for many years. Studies of large series have also failed to distinguish persons apt to have recurrent stones from those in whom stones occurred only once (with regard to biochemistry of serum and urine, composition of stone, urinary infection or need for surgical operations).[3] Ljunghall and Hedstrand[3] found that a positive family history was significantly correlated with multiple recurrences, and that, as other investigators had noted,[4-6] a family history of kidney stones is more common for patients with stones than for persons in a control population. This has been attributed to both environmental and genetic factors[3-6] that predispose a person to the formation of renal calculi.

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Pathogenesis

Although it is not possible to indicate the exact pathogenesis of kidney stones in most patients, the situation is not hopeless. It is possible to set up an orderly scheme that will include all or almost all of the fundamental pathogenic factors involved in the formation of a clinically evident renal calculus, and apply it to patients.[7] Figure 1 by Vermeulen[7] represents diagrammatically all

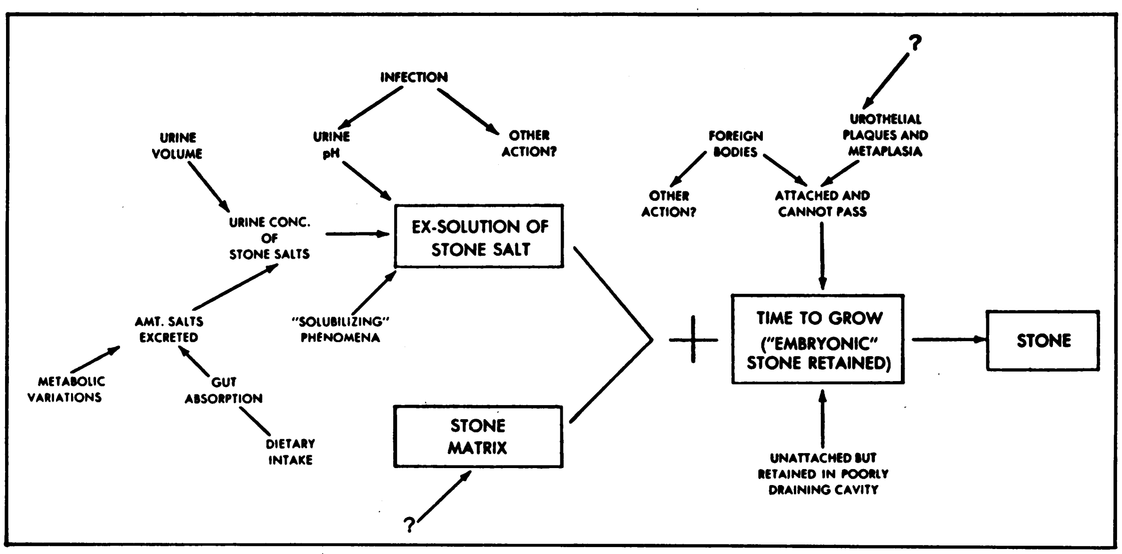

Figure 1.—Summary view of factors cooperating in urinary stone formation. (From Vermeulen[7]; reproduced by permission from University of Chicago Press.)

the known factors involved in urinary stone formation. The final stone at the far right in the diagram represents any type of renal calculus. To the left, the concentration of the salt (or salts) or compound making up the stone is a function of the amount excreted and the rate of urine flow. The amount excreted depends on the dietary intake, its absorption by the gut and metabolic (endogenous) factors responsible for its formation, such as uric acid, or enhanced renal excretion (decreased tubular reabsorption of cystine).

It is axiomatic that the larger the urine volume, the lower will be the concentration of the constituents of the stone, and the less the propensity for crystallization from a supersaturated solution (and vice versa).[8,9] Hodgkinson[10] reported that cystine, uric acid and magnesium ammonium phosphate stones are readily explained in these terms: cystine stones are caused by oversaturation of the urine with cystine; uric acid stones by excessive excretion of uric acid or excessive urinary acidity (both of which lead to oversaturation of the urine with uric acid), and magnesium ammonium phosphate stones by liberation of ammonium ions from urea. This occurs by urea-splitting organisms leading to a rise in urine pH and oversaturation of the urine's content of magnesium ammonium phosphate. Thus, urine concentration, infection and urinary pH (Figure 1) are important factors in the crystallization of a supersaturated solution. The degree of saturation of a solution is determined by comparing the ionic activity product with the known solubility and formation products of the relevant solute. Solutions having activity products below the solubility product are said to be undersaturated and any crystals of the solute will tend to dissolve. Above the solubility product, there is a region of metastable supersaturation in which a solution can exist for relatively long periods without crystallization occurring, although formation of crystals can be induced by the addition of a suitable nucleus. Above the formation product, spontaneous nucleation can occur and crystal growth is usually rapid.[10]

The above principles have been applied for many years to studies of the solubility of the major divalent ion salts and other stone-forming

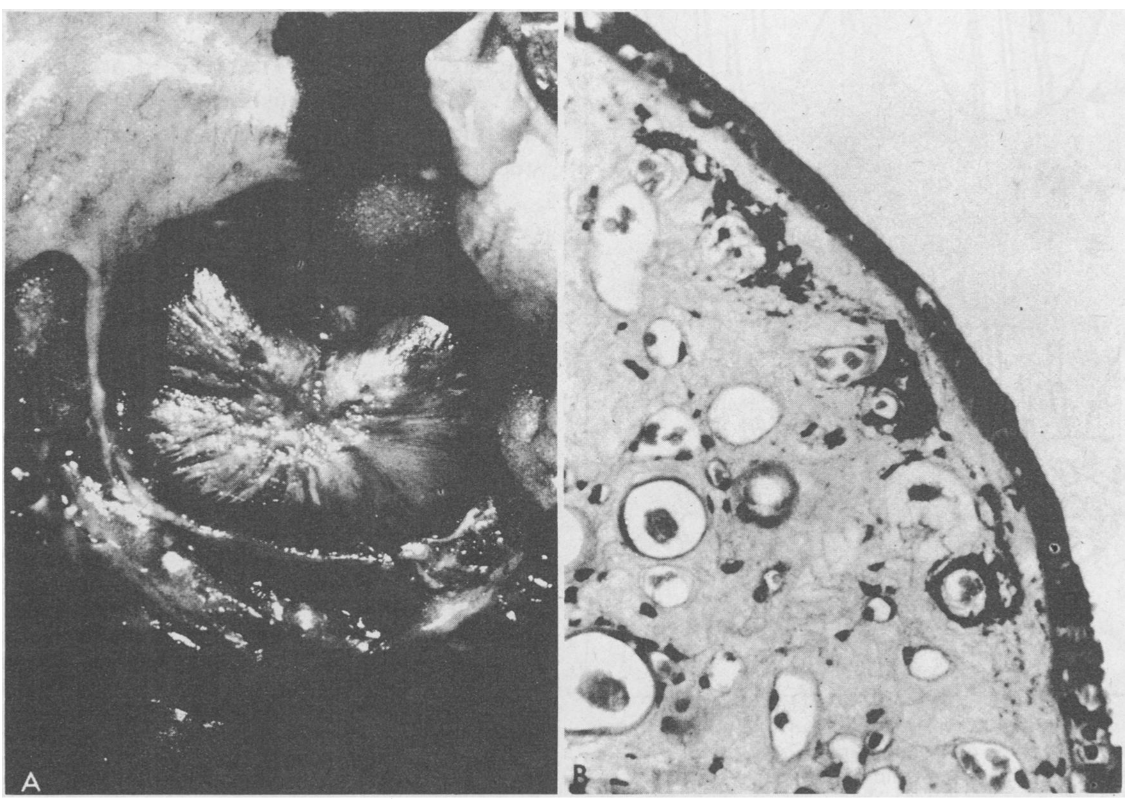

Figure 2.—Randall plaques. **A,** Papilla with Randall plaques viewed from above. **B,** Section of a Randall plaque showing calcification around capillaries in subepithelial plane (Hematoxylin and eosin stain; reduced from magnification ×250). (From Burry et al[19]; reproduced by permission from Human Pathology.)

solutes in human urine.[7-12] They have shown that normal urine contains potent inhibitors of calcium oxalate and calcium phosphate crystal growth, one or more of which may be deficient in the urine of persons in whom stones form.[9-13] Vermeulen[7] refers to these inhibiting substances as "solubilizing" phenomena or materials that by their presence impede or prevent stone salts from passing from the dissolved to the solid state, termed "ex-solution" (Figure 1). Citrates, pyrophosphates, magnesium and phosphocitrates[12] have been shown to have considerable inhibiting properties in the concentrations usually found in human urine. However, taking each separately, it is not clear whether their concentrations in urine differ significantly between persons in whom stones form and those in whom stones do not form. Despite this, the urine of a patient with calcium oxalate stones, the most common type

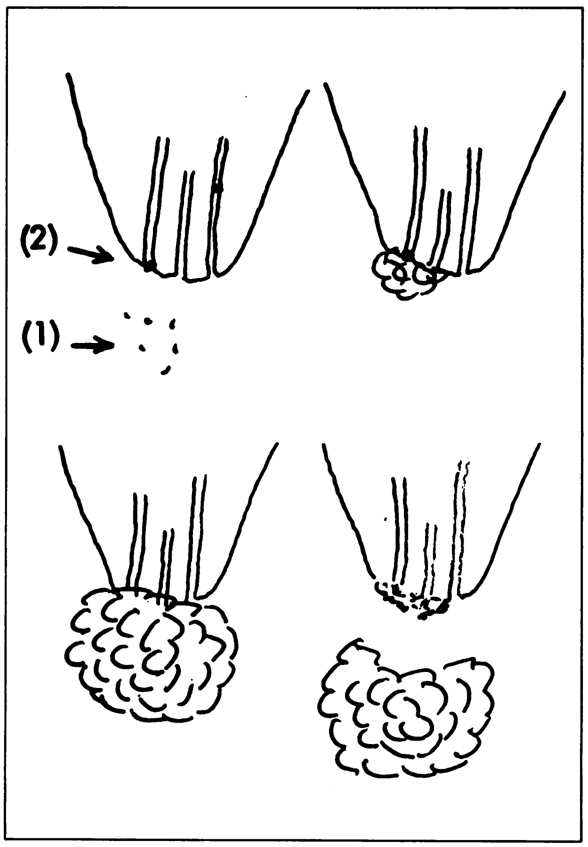

Figure 3.—Schematic representation of embryogenesis and crystal growth on renal papilla beginning with formation of potential embryonic stones in collecting ducts. Many abort into pelvis (1), but one is shown caught at duct ostium (2). Retained embryonic stone, now exposed to pelvic urine, continues to grow and finally sloughs away or fragments. (From Vermeulen et al[18]; reproduced by permission from Journal of Urology.)

of kidney stone in the Western world, is deficient in urinary-inhibiting activity against crystallization of calcium oxalate.[10,11]

In Vermeulen's diagram (Figure 1) organic matrix of the stone is given a prominent position because some nidus of proteinaceous material, even of a minimal amount (5 percent of the stone's weight), is found in almost all of the common renal stones.

This organic material may be derived from the site on the renal pyramid or calyx where the initial abnormal crystallization or crystal aggregation is occurring.[7,8,14] Oversaturation of the urine with certain chemical constituents and defective inhibitory activity provide a rational explanation for the nucleation and a subsequent growth of many submacroscopic or embryonic stones.[9-14] However, it is difficult to conceive of the stone growing to macroscopic size simply de novo in the free flowing urinary stream. More likely, a site of microscopic tissue degeneration or abnormality on either the tip of the medullary pyramid or on the minor calyceal epithelium, serves as the organic nidus to which the crystals will adhere, and grow to sufficient size without being washed "downstream and out" in the excreted urine.[7,8,14] Time is also a factor (Figure 1): "A stone obviously requires time to grow to significant size and it can so grow only if it is retained in the urinary tract."[7]

Many years ago Randall[15-17] developed a concept relating growth of the embryonic stone to the renal papilla. Vermeulen and associates[18] summarized Randall's concept and we quote from their paper:

> According to his view, the stone process could begin in a seemingly normal urinary tract only because an unrecognized abnormality was, in fact, present—an antecedent lesion of the renal papilla. In a series of more than 1,100 autopsies he found minute surface patches or plaques on the papilla in more than 19 percent of the kidneys examined. He concluded that these surface defects acted as stone growth centers since small stones were occasionally attached to them. Randall believed that the plaques were small areas of subepithelial calcification; perhaps the result of antecedent infection, a toxic agent, or some kind of minute vascular disturbance leading to necrosis beneath the urothelium. Later the plaque was denuded of its epithelial covering so that the calcified tissue was now exposed to the pelvic urine and could behave as a foreign surface attracting crystallization and stone formation upon itself.

Subsequent publications have confirmed Randall's findings and, most recently, Burry and colleagues[19] reviewed the entire subject and presented additional confirming data. Figure 2[19] shows the gross and microscopic appearance of the plaques discussed by Randall in the human kidney. Figure 3 offers a schematic representation of embryogenesis and growth on renal papilla; Figures 4 and 5 illustrate clinical findings of stone formation.[18]

The final product of the metabolic, physiochemical and abnormal cooperating factors, the clinically evident stone (Figure 1), may appear as an asymptomatic finding on a kidney, ureter and bladder (KUB) study or on an intravenous pyelogram (IVP) done for other purposes. These might include a diagnostic follow-up of abnormal urinary sediment; an attack of renal colic; an episode of gross hematuria or acute urinary tract infection, or part of a clinician's workup of a patient with positive risk factors for nephrolithia-

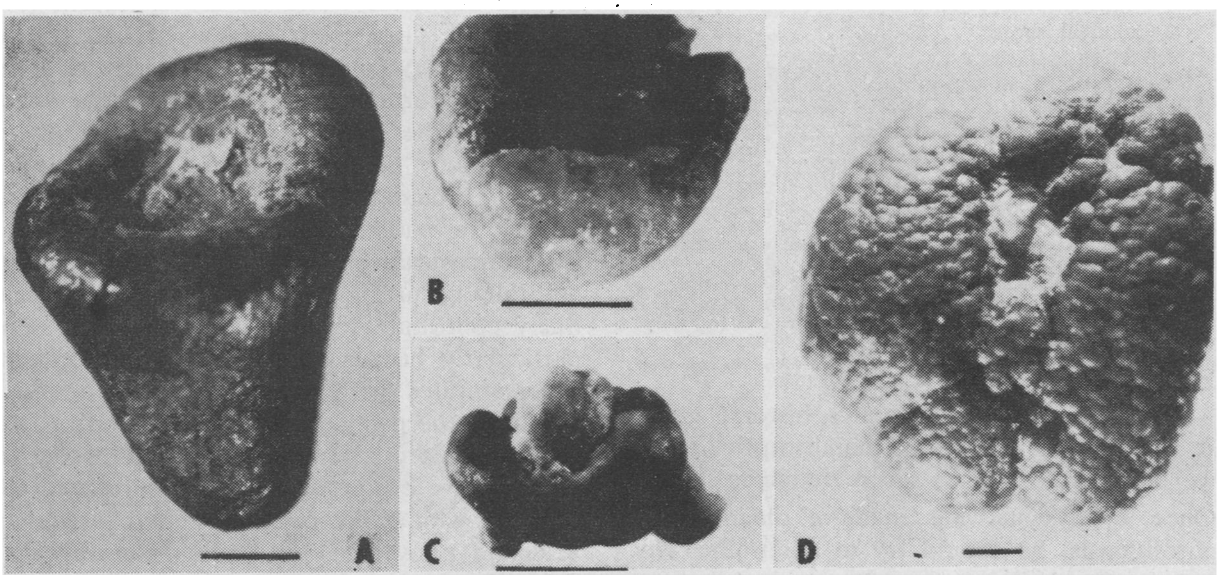

Figure 4.—Small human oxalate calculi. **A** and **B**, Concave surfaces suggest formation upon papillary tip. **C**, Central crystalline pedicle (oxalate) within concavity. **D**, A larger stone with central dimple and small pedicle; white material in dimple is apatite (measuring bars equivalent to 1 mm). (From Vermeulen et al[18]; reproduced by permission from Journal of Urology.)

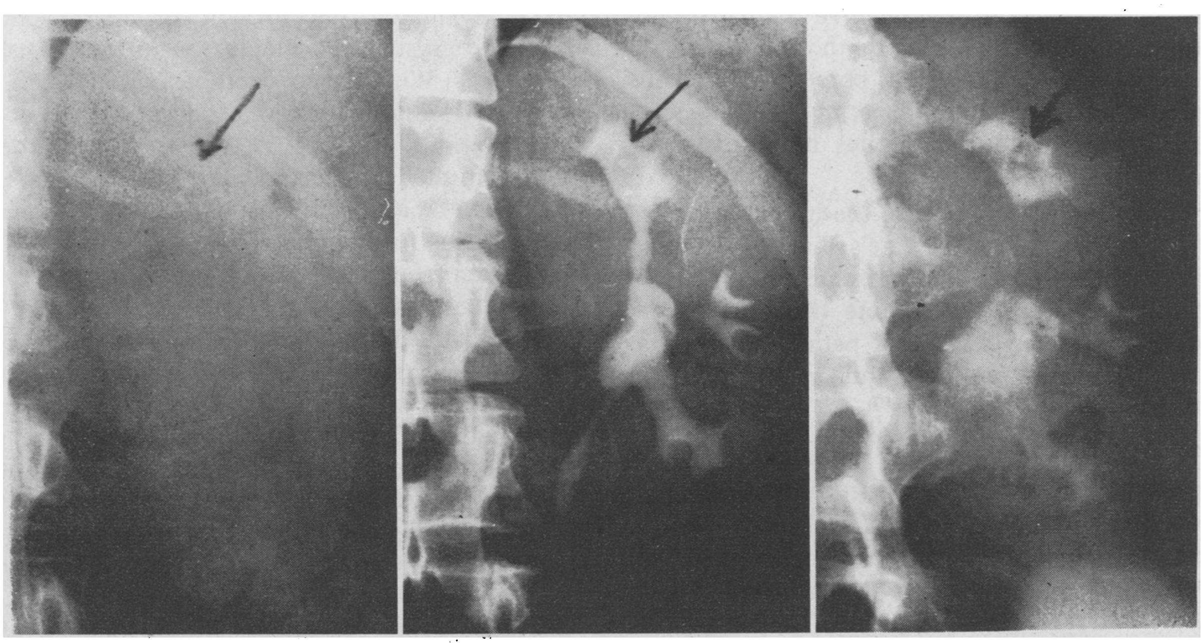

Figure 5.—Pyelgrams of a patient's kidney. Arrows show minute calcification in or on renal papilla; film with oblique projection on right. (From Vermeulen et al[18]; reproduced by permission from Journal of Urology.)

TABLE 1.—*Diagnostic Classification of 230* Consecutive Patients with Renal Stones†*

Diagnosis	*Patients*
Uric acid stones	9
Renal tubular acidosis	9
Medullary sponge kidney	16
Primary hyperparathyroidism	10
Sarcoidosis	4
Hyperthyroidism	2
Vitamin D or calcium excess	2
Inflammatory bowel disease	9
Chronic diarrheal states	7
Jejunoileal shunts	2
Infection	8
Cystinuria	3
Alkali abuse	2
Acetazolamide administration	1
Idiopathic calcium stones‡	146
TOTAL	230

*Only 84 (37 percent) of the 230 patients had well-established disease.

†Data from Coe and Kavalach.[20]

‡In 14 patients there were some stones composed of uric acid mixed with calcium oxalate; however, calcium oxalate stones were the predominant stones formed.

sis (for example, strong family history, gouty trait, hypercalcemia, chronic malabsorptive small bowel disease, fasting or severe reducing diets).

Once a physician has made a diagnosis of nephrolithiasis, he should try to determine why the stone developed and what can be done to prevent new stone formation. A knowledge of the relative frequency of the various causes is of basic importance. Table 1 lists the diagnostic classification of 230 *consecutive* patients with renal stones[20]; it is similar to the experience in most clinics. More than 50 percent of patients have idiopathic calcium stones; about 40 percent of patients with calcium stones have idiopathic hypercalciuria.

In this clinical conference, the major causes of stone formation listed in Coe's diagnostic classification (Table 1) will be presented. We hope to end this conference on a note of optimism regarding our understanding of pathogenic mechanisms, diagnosis, treatment and, most important, prevention.

Dr. Coburn will discuss patients in whom calcium oxalate stones (one of the most common types of kidney stone) form. Although he will focus primarily on patients who do not have hypercalciuria or hyperparathyroidism, the physiochemical mechanisms of stone formation that he will discuss may apply to patients with these diagnoses as well.

Calcium Oxalate Stones—Pathogenesis, Clinical Problems and Treatment

JACK W. COBURN, MD*

MANY PATIENTS with renal calculi that contain calcium have idiopathic hypercalciuria or a parathyroid adenoma; however, in 40 percent to 50 percent of those with typical calcium oxalate stones, urinary calcium excretion may be within a defined "normal range."[21,22] An excess concentration of the constituent solutes, calcium and oxalate, may contribute to the pathogenesis of stones. Calcium stones occur with increased frequency in patients whose primary problem is hyperuricosuria or cystinuria. Deficiency of a naturally occurring inhibitor of precipitation may likely contribute to the pathogenesis of stones, particularly because normal urine is commonly supersaturated with oxalate.

During the past several years, Robertson, Peacock and Nordin,[9] from Leeds, and Pak,[23] from Dallas, have evaluated the role of the saturation of urine with either calcium oxalate or brushite (calcium phosphate) as factors contributing to the pathogenesis of stones. The English workers calculated the saturation products from the various ionic strengths, the urinary pH and the formation constants for various calcium complexes.[9] Pak[23] evaluated the growth or regression of synthetic crystals of calcium oxalate or brushite in urine. With these methods, urine can be characterized as containing oxalate at levels above the solubility product, at which point urine is supersaturated and crystal growth (but not new formation) can occur. At higher solute concentrations, the formation product (a point of supersaturation from which precipitation of new crystal may occur) is reached.

When the formation product for calcium oxalate was evaluated in urine specimens from normal subjects and from those in whom recurrent renal stone formation occurred, there were statistical differences between the means of the two groups; however, considerable overlap existed for individual subjects.[11] Values for most urine specimens from normal subjects were either supersaturated or exceeded the formation product. In the same urine specimens, Robertson and asso-

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ciates[11] tested for the presence of inhibitory substances by measuring the growth of seed crystals of calcium oxalate in a standard supersaturated solution with and without addition of a small volume of test urine; thus, the degree of retardation of crystal growth was quantitated. Urine from patients with recurrent stone formation was found to inhibit less growth than urine from normal subjects. Nevertheless, considerable overlap existed between the two groups. When the effects of both the activity product and inhibitory capacity were evaluated, a distinct difference was noted between the urine specimens from patients in whom stones recurred and those from normal subjects. They calculated a "line" that best separated the two groups and estimated the combined contribution of a formation product and the extent of inhibitory factors as the distance from the line, a characteristic termed the saturation-inhibitor index. This index provided good separation between the values of the urine specimens from patients with renal stones and those from normal subjects. Such observations suggest that urinary concentrations of calcium and oxalate, and reduced presence of unidentified inhibitors of calcification, contribute toward the pathogenesis of stones.

Certain inhibitors of crystal formation may exist in urine, including pyrophosphate, magnesium, various amino acids, certain trace elements and some values of urine pH. Of these, pyrophosphate is a highly potent natural inhibitor of crystal formation; however, the concentrations of pyrophosphate are not reduced in the urine of those in whom renal stones are formed. Thomas and Howard[24] characterized urine as being "good" or "evil" based on its capability to inhibit the calcification of rachitic rat cartilage. It has recently been suggested that phosphocitrate may be responsible for inhibition of calcification.[12] Nevertheless, it has not been possible to classify or identify patients with idiopathic renal stone formation on the basis of the presence or absence of a specific inhibitor in their urine.

Diphosphonates may be used potentially as therapeutic agents in stone disease; they are chemically synthesized analogs of pyrophosphate, which are not subject to degradation by naturally occurring pyrophosphatases.[25] In solutions of synthetic urine, the diphosphonates are highly effective in preventing crystal growth.[25] However, the amount of diphosphonates required to prevent urinary stone formation may lead to abnormal skeletal mineralization.[26,27] The future clinical application of these compounds remains uncertain.

Of all the constituents present in urine, oxalate is one that is most likely to induce serious and recurrent nephrolithiasis, especially when its concentration is increased. There is disagreement about the role of augmented oxalate in contributing to stone formation, except under unusual circumstances. The amount of urinary oxalate has been found to be normal in most patients with renal stones.[28] However, others have noted that many persons in whom idiopathic stone formation occurs may show periodic increases in urinary oxalate.[29,30] Oxalate is produced as an end product of glycine metabolism, which cannot be metabolized; it arises from glyoxylate or glycolate. Increased oxalate excretion in the urine can occur because of increased generation of its precursors or because of inhibition of the pathways whereby glyoxylate or glycolate are converted to compounds other than oxalate.

Two forms of primary hyperoxaluria exist; they are usually manifested by recurrent stone formation with progressive renal failure in childhood or adolescence.[31] Acquired hyperoxaluria occurs most commonly as a consequence of disease of the small intestine; it is present in 7 percent to 30 percent of patients after resection of the ileum or an intestinal bypass operation for extreme obesity.[32,33] Although the mechanism is not certain, hyperoxaluria is believed to occur because of extensive absorption of oxalate. It has been postulated that calcium is poorly absorbed because of the formation of calcium soaps in the intestinal lumen. Normally, calcium present in the intestinal lumen precipitates as insoluble calcium oxalate, which is nonabsorbable. With the binding of calcium to soaps, a larger fraction of oxalate is free and can thus be absorbed.

The addition of oxalate to the diet of patients with hyperoxaluria substantially augments urinary oxalate compared with a small increment in oxalate that occurs after the same addition of oxalate to the diet of normal persons.[34] The management of these patients should include a reduction of the dietary intake of oxalate. Foods that are high in oxalate content, such as spinach, mustard greens, Swiss chard, other leafy green vegetables, rhubarb and tea, should be avoided. The administration of cholestyramine, which may modify bile salts and render oxalate nonabsorbable, may also reduce urinary oxalate excretion under certain conditions. Earnest, Williams and Admirand[35] have reported that the administration of calcium salts can lead to a substantial fall in urinary oxalate excretion. Recurrent renal calculi and renal failure caused by oxalosis are serious complications of intestinal bypass operations and the "vanishing bowel" syndrome associated with ileal disease; such patients should have periodic assessment of urine oxalate and renal stone formation to avoid serious and irreversible complications.

Many patients with recurrent calcium oxalate stones have increased amounts of uric acid in plasma and urine; however, the stones may contain no uric acid. Recently, Coe and colleagues,[36] and Pak and Arnold[37] found that the addition of sodium urate (but not uric acid) to artificial solutions containing calcium and oxalate enhanced the precipitation of calcium oxalate. This finding provides a basis for the empiric observation that the administration of allopurinol is effective in reducing the prevalence of nephrolithiasis in patients with hyperuricosuria and calcium oxalate stones.

With this background, available means for managing patients with urolithiasis caused by calcium oxalate can be reviewed. Two of the major principles of management are reduction in dietary calcium uptake and intake of copious quantities of fluid. Indeed, compliance to such a regimen may explain why several workers have noted that the prevalence of stones decreases in patients who are followed regularly in a clinic that specializes in kidney stones[20] and by physicians who are interested in urolithiasis. Cellulose phosphate, which decreases intestinal calcium absorption by binding calcium in the intestine and rendering it nonabsorbable,[38] can substitute in part for reduced calcium intake. Although reduced intestinal absorption may contribute to osteoporosis or secondary hyperparathyroidism, there are no data indicating that this risk is great.[39] Urinary oxalate levels increase during treatment with cellulose phosphate.[40] This agent remains an investigational drug in the United States, although it has been used in the United Kingdom.

The thiazide-type diuretics make up a group of drugs that reduce urinary calcium excretion and thereby reduce the incidence of stones.[41] These agents reduce urinary calcium excretion due, in large part, to a contraction of extracellular volume, which augments more proximal tubular reabsorption of sodium, calcium and other solutes.[42] In the distal nephron, these diuretics inhibit distal tubular calcium reabsorption to a very small extent compared with a major effect on sodium reabsorption.[43] These agents can reduce the urinary calcium excretion in normal persons as well as in patients with hyperparathyroidism and idiopathic hypercalciuria. To achieve a desired effect, dietary sodium intake should be moderately decreased, that is, below 7 to 10 grams (100 to 150 mEq) of sodium per day.

Edwards and associates[44] have reported the successful management of urolithiasis by ingestion of neutral salts of orthophosphate. However, other investigators, using a slightly lower dose, found no benefit in a double-blind controlled study.[45] The mechanism whereby orthophosphate can reduce the occurrence of stones is not entirely clear. Usually, there is a decrease in urinary calcium excretion, and pyrophosphate excretion may increase; the latter could reduce stone formation by acting as an inhibitor of crystal formation. Finally, the oral administration of magnesium, which may act as an inhibitor of calcification, may be considered an adjunct in the management of certain patients with renal stones disease.[46]

At present, it is possible to reduce greatly the incidence of stones or to prevent their recurrence with use of these therapeutic modalities. Therefore, empiric therapy, which is aimed at reducing the quantities of calcium (or oxalate) in the urine, or the addition of an inhibitor may be effective in managing recurrent nephrolithiasis, despite a lack of knowledge of the pathogenesis of renal stone disease.

DR. KLEEMAN: *Studies in outstanding "stone" clinics show that nearly all patients in whom idiopathic stones are formed have hypercalciuria; and, within this group, there are a few cases of primary hyperparathyroidism. Doctor Brickman will report on the causes of hypercalciuria in these patients.*

Idiopathic Hypercalciuria in Patients with Kidney Stones

ARNOLD S. BRICKMAN, MD*

MANY PERSONS with calcium-containing kidney stones seem to excrete excessive amounts of calcium in the urine. Although few patients may

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show signs of clinically overt primary hyperparathyroidism, most of them fit into a loosely characterized group, originally designated by Albright and associates[47] as having idiopathic hypercalciuria. At present, the favored view is that hypercalciuria is a common expression of perhaps several distinctive metabolic disorders affecting primarily the intestine or the kidney.

There are three predominant theories about the pathogenesis of hypercalciuria: (1) the primary intestinal defect hypothesis (absorptive hypercalciuria), (2) the "renal calcium leak" hypothesis (renal hypercalciuria) and (3) the "renal phosphorus leak" hypothesis.

Intestinal Defect Theory

Intestinal hyperabsorption of calcium has been documented as a frequent finding in patients with kidney stones and with hypercalciuria.[48-51] However, the occurrence of augmented calcium absorption, although possibly a primary phenomenon, is predicted in both the renal calcium and phosphorus leak hypotheses as a secondary event. In both of these theories, intestinal absorption of calcium occurs as a consequence of enhanced conversion of 25-hydroxycholecalciferol (25-OH-D_3) to 1,25-dihydroxycholecalciferol (1,25-$[OH]_2D_3$) either by the stimulus of hyperparathyroidism or by a lowered level of serum phosphorus.[52-54] Thus, the presence of enhanced intestinal absorption of calcium alone cannot be used to distinguish the pathogenesis of hypercalciuria. In patients with a hypothetical primary disorder of intestinal calcium transport, hypercalciuria occurs as a consequence of an augmented filtered load of calcium to the kidney and the secondary suppression of parathyroid hormone action. The latter results from the slightly raised levels of serum calcium attributable to increased intestinal absorption. Another feature, which has been used to characterize patients with primary absorptive hypercalciuria, is a normal urinary calcium:creatinine ratio after a 12-hour to 14-hour fast.[55] Bordier and co-workers[56] have also suggested that when diets low in calcium content are ingested, patients with absorptive hypercalciuria may have lower levels of urinary calcium excretion than those with renal calcium or phosphorus wasting; however, relative hypercalciuria is present in all three groups. Therefore, evidence for primary absorptive hypercalciuria[55,56] includes augmented intestinal absorption of calcium, normal levels in serum of calcium and phosphorus, normal to low levels of parathyroid hormone, normal urinary excretion of cyclic adenosine-3′,5-monophosphate (AMP), and a normal fasting urinary calcium: creatinine ratio.

The nature of the hypothetical intestinal defect is not known. Kaplan and colleagues[57] have reported elevated levels of circulating 1,25-$(OH)_2$ D_3 in some patients with apparent absorptive hypercalciuria as characterized by the above criteria. Thus, overproduction of this sterol could explain enhanced intestinal absorption; however, it seems to exclude the intestine as the site of the primary defect. A second explanation could be altered intestinal sensitivity to 1,25-$(OH)_2D_3$. This hypothesis could explain the finding of normal levels of 1,25-$(OH)_2D_3$ in some patients with absorptive hypercalciuria.[57,58] Finally, the enhanced intestinal absorption of calcium may not be vitamin D-mediated.

Renal Calcium Leak Theory

Several investigators have suggested the presence of decreased renal reabsorption of calcium as an explanation for hypercalciuria in patients in whom stones form. In early studies, Edwards and Hodgkinson[59] reported an elevated clearance of calcium in 14 patients with hypercalciuria. They also found that an elevated urinary calcium:creatinine ratio occurred in some fasting patients in whom stones occurred, and interpreted this as indicating a renal wasting of calcium. Pak and associates[55] found this defect in 2 of 30 patients, whereas Coe and colleagues[60] and Bordier and colleagues[56] (both groups of investigators relying mainly on the findings of normocalcemic hyperparathyroidism) found a renal calcium leak in 26 of 40, and in 22 of 71 patients, respectively. Coe and associates[60] have suggested that the renal calcium leak hypothesis could be tested by examining the effect of suppression of hypercalciuria on the elevated levels of parathyroid hormone. They reported that the reduction of urinary excretion of calcium by hydrochlorothiazide therapy resulted in suppression of hyperparathyroidism in patients with stones and mild hypercalciuria. In contrast, administration of furosemide to normal volunteers resulted in a calciuric response associated with a rise in parathyroid hormone. Other workers have found thiazide-induced suppression of intestinal absorption of calcium in these patients.[61,62] At present, additional evidence supporting defective renal tubular handling of filtered calcium is lacking.

The nature of the putative defect in renal calcium handling is unknown. Lemann, Piering and Lennon[63] found exaggerated calciuric and magnesuric responses to oral or intravenous administration of glucose loads after overnight fasting in patients in whom stones occurred. However, these investigators did not attempt to subclassify their patients according to possible pathogenesis of hypercalciuria.

Renal Phosphorus Leak Theory

Of the three theories discussed, this is the most recent, having evolved mainly as a consequence of continuing advances in our understanding of vitamin D metabolism. The tendency toward low levels of serum phosphorus or frank hypophosphatemia has been recognized as a frequent finding in patients with hypercalciuria.[47,64,65] Several workers have emphasized the finding of slightly enhanced fractional excretion of phosporus or a decreased threshold for phosphorus excretion (tubular maximum for phosphorus transport/glomerular filtration rate [TMP/GFR]).[56,66] Llach and co-workers[67] also described augmented renal clearance of phosphorus during acute phosphorus loading in a few patients. According to the renal phosphorus leak theory, hypophosphatemia, occurring as a consequence of renal loss, stimulates production of 1,25-$(OH)_2 D_3$, resulting in augmented intestinal absorption of calcium. Hypercalciuria results from the enhanced filtered load of calcium and mild suppression of parathyroid hormone. In this theory the development of hypercalciuria is analogous to that found in states of phosphorus depletion in humans. Dominguez, Gray and Lemann[68] have shown increased metabolism of 25-$(OH)D_3$ to 1,25-$(OH)_2D_3$ in experimental phosphorus depletion in humans. Gray and associates[69] have also reported an inverse relationship between the decrease in serum phosphorus and increase in plasma levels of 1,25-$(OH)_2D_3$ during phosphorus depletion.

If each of these theories of pathogenesis—intestinal defect theory, renal calcium leak theory and renal phosphorus leak—proves to be correct, and if the population of patients with so-called idiopathic hypercalciuria is made up only of patients with these disorders, then considerable overlap in their biochemical features exists. Thus, augmented intestinal absorption of calcium would be predicted for each type of patient; normal to suppressed circulating levels of parathyroid hormone would be predicted for patients with both absorptive hypercalciuria and with a primary renal phosphorus leak. Elevated levels of parathyroid hormone have been reported in patients with a proposed renal calcium leak, but they also occur in patients with so-called normocalcemic primary hyperparathyroidism.[70] In this brief review we shall not consider the latter disorder. However, the close similarity between this entity and the features described in patients with renal hypercalciuria has suggested to some investigators a causal relationship between chronic secondary hyperparathyroidism and the development of autonomous parathyroid function due to hyperplasia or the development of a tumor. Thus, the careful and systematic investigation of mineral homeostasis in stone-forming patients, together with standardization of definitions of hypercalciuria and measurements of parathyroid hormone and vitamin D analogs, is helping the categorization of patients; this should provide insights into pathogenetic mechanisms.

DR. KLEEMAN: *Although patients with uric acid calculi constitute only a small proportion of the total population of those in whom stones form, they represent a group in whom good medical therapy has proved most successful. It is therapy based on sound physiologic principles. Dr. David Lee will bring us up to date on patients with uric acid stone formation.*

Uric Acid Calculi

DAVID B. N. LEE, MD*

THE OLDEST RENAL STONE in present-day collections contains a uric acid nucleus. It was recovered from the mummy of an Egyptian who had died more than 7,000 years ago.[71] Uric acid causes about 10 percent of all stones that are found in patients in United States.[72] The prevalence of uric acid lithiasis varies with racial background and geographic location. The highest incidence has been recorded in Israel, where in one large series of patients with urinary calculi, 39.5 percent had uric acid stones.[73] Lange[74] has traced the phenomenon of increased incidence of kidney stone formation in Germany since 1945; the frequency of patients with uric acid stones in various German clinics rose from 4.1 percent in 1958 to

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23 percent in 1965, with one clinic reaching an all-time high of 40 percent.

The formation of uric acid stones is attributed primarily to precipitation of uric acid from oversaturated urine. The degree of oversaturation and, therefore, the tendency towards uric acid precipitation is not only determined by the volume of urine and the amount of uric acid excreted, but is also critically dependent on the urinary pH. Although uric acid is almost insoluble in water, in a buffer solution (such as urine) its solubility increases as the pH rises, a result of its dissociation into urate ions.[72,75] Uric acid lithiasis either may occur in the absence of hyperuricosuria (by reduction in urine volume or urine pH or both) or may not occur in hyperuricosuria (by increasing urine volume or urine pH or both). These considerations are of fundamental importance in the clinical approach to problems related to uric acid calculus disease. Sperling and de Vries,[76] together with Kedem[77] explored the possibility that patients with uric acid lithiasis may form qualitatively abnormal urine that lacks the supersaturation-maintaining capacity for uric acid; however, their findings did not support the concept.

TABLE 2.—*Clinical Classification of Uric Acid Nephrolithiasis*

Uric acid nephrolithiasis not associated with hyperuricemia or hyperuricosuria.

- Idiopathic
  - Sporadic[72,75]
  - Familial[73,78]
- Excessive dehydration
  - Loss through skin[73]
  - Loss through intestine[81-84]

Uric acid nephrolithiasis associated with hyperuricemia with or without hyperuricosuria.

- Gout[73,75,76]
- Myeloproliferative, neoplastic, hemolytic disorders[87-92]
- Enzyme abnormalities
  - Hypoxanthine-guanine phosphoribosyltransferase (HGPRTase) deficiency: Complete (Lesch-Nyhan syndrome)[95] and partial (? variety of primary gout)[96]
  - Glucose-6-phosphatase deficiency (type 1 glycogen storage disease)[97]
  - Glutathione reductase variant[98]
  - Phosphoribosylpyrophosphate amidotransferase variant[99]
  - Mutants of phosphoribosylpyrophosphate (PRPP) synthetase[100]

Uric acid nephrolithiasis associated with hyperuricosuria without hyperuricemia.

- Excessive protein and purine ingestion[72]
- Defect in tubular reabsorption of uric acid
  - Uricosuric drugs[72]
  - Congenital or acquired defects[72,104,105]

Table 2 is adapted from published information[72,75] and represents an attempt to classify uric acid lithiasis encountered in clinical practice into broad categories. For this purpose, hyperuricemia is defined as a serum uric acid concentration of more than 6.5 mg per dl in men and 5.5 mg per dl in women; hyperuricosuria is defined as a urinary uric acid excretion of more than 800 mg per day on an average unrestricted diet.[72] The definitions of these values are arbitrary. This classification will undoubtedly undergo repeated modifications and is intended only to be used as a convenient reference framework.

Most patients with uric acid stones have neither hyperuricemia nor hyperuricosuria and fall under the diagnostic category of idiopathic uric acid lithiasis. This abnormality may occur sporadically or may be transmitted in an autosomal dominant pattern.[73,78] The proportion of women in this group (27.5 percent) is much higher than that found in persons with gout in whom uric acid kidney stones form (8.6 percent).[72] Henneman, Wallach and Dempsey[79] reported, however, that this disorder affected both sexes with equal frequency. The only physiologic deviation present in these patients is a persistently low urinary pH, which remains fairly constant (below 5.4) with little variation through the day. The normal late-morning and postprandial "alkaline tides" (marked by a rise in urinary pH to more than 6.0) are absent in these patients. This inability to increase urinary pH is considered important in the precipitation of uric acid in the urinary tract, even though the quantity of uric acid excreted is not excessive. Decreased ammonia formation has been proposed by some investigators,[72,79] and refuted by others[75,80] to be important in the development and maintenance of urine with an inappropriately low pH.

Increased prevalence of uric acid stones in persons working in arid and parched areas has been attributed to severe reduction in urine volume. Atsmon, de Vries and Frank[73] pointed out that in desert regions a fluid intake of 10 to 15 liters may be necessary to maintain a daily urine volume of one liter.[77] Uric acid stones are also seen in patients with ulcerative colitis, regional enteritis and ileostomies.[81-84] Low urine volume, increased uric acid excretion and systemic metabolic acidosis with excessively acidic urine[83,84] have all been considered important in the development of uric acid stones in these diarrheal states.

Uric acid stones may develop in patients with hyperuricemia with or without concomitant hyperuricosuria. In about 20 percent of patients with primary gout in the United States uric acid lithiasis occurs[72]; in Israel, the incidence of uric acid stones in persons with gout is as high as 75 percent.[73] The difference may be attributed to several factors including variations in racial background, climate and geographic location. In addition, the diagnostic criteria for primary gout are also not uniform.[75] Both hyperuricosuria and acidic urine have been considered important predisposing factors in uric acid stone formation in patients with gout. However, most patients (70 percent) with gout do not excrete excessive uric acid in the urine.[72] Also, in patients with gout, only 47 percent of those in whom stones form and as many as 28 percent of those in whom stones do not form, have persistently acidic urine.[85] Nephrolithiasis may precede the first development of acute arthritis, in some cases by more than a decade.[72,86]

Hyperuricemia and hyperuricosuria may result from an increase in cellular nucleic acid metabolism by excessive production or destruction of cells. Clinical examples include polycythemia vera, myeloid splenomegaly, myeloid leukemia, myelomas and sickle cell anemia.[87-92] Vigorous cytolytic therapy in these conditions may lead to fulminant hyperuricemia (more than 50 mg per dl has been documented in patients with leukemia). Pronounced hyperuricemia may result in the development of acute renal failure[93] attributed to precipitation of uric acid and urate in both the collecting ducts and the renal vascular complex.[94]

Several enzyme abnormalities have been documented in patients with hyperuricemia,[95-102] in whom there is a high occurrence of uric acid lithiasis. Hyperuricosuria[101] and low urine volume[102] are considered important factors in the causation of stone formation in these patients.

The last group of patients with uric acid lithiasis is characterized by hyperuricosuria without overt hyperuricemia. Excessive consumption of protein and purine is an often quoted example. The surplus uric acid formed is rapidly cleared by the kidneys causing no perceptible changes in serum uric acid concentration.[72] Use of uricosuric agents is another cause of increased urinary uric acid. In 16 percent of patients with gout in whom uric acid lithiasis developed, stone formation was attributable to the liberal intake of uricosuric agents.[72]

An inborn defect in renal tubular handling of uric acid and hyperuricosuria is believed to be the cause for the high prevalence of uric acid lithiasis seen in the dalmatian coachhound.[103] A similar inborn defect in renal tubular handling of uric acid has been shown in humans.[104,105] Increased uric acid excretion may also occur as part of a generalized defect in tubular function—the renal Fanconi syndrome. The absence of uric acid lithiasis in these conditions may be due to the concomitant bicarbonate wastage and the development of renal tubular acidosis.[72] The interrelationship between hyperuricosuria and recurrent idiopathic calcium nephrolithiasis is discussed by Dr. Narins in this symposium.

Clinical Features

Patients with uric acid lithiasis usually complain of passage of reddish sand, gravel or stone. The history may include recurrent colic, urinary obstruction and infection. A history of gout in the patient or in the family members, or both, is present in some cases. Persistently low pH and the presence of uric acid crystals in repeated analysis of urine are helpful diagnostic findings. Hyperuricemia or hyperuricosuria, or both, may be present, although in many patients with uric acid lithiasis both features may be absent. Findings on intravenous pyelography show a radiolucent shadow or shadows. The differential diagnosis for exclusion includes cystine stone and tumor.[72,75]

Treatment

The development of rational and effective treatment for uric acid stones has virtually eliminated the necessity for surgical operations in these patients. Effective treatment consists of (1) decreasing urinary uric acid concentration by increasing urine volume (high fluid intake) and decreasing uric acid production and excretion (allopurinol administration); and (2) increasing uric acid solubility by increasing urine pH (alkalinizing medications). If the patient is not ingesting excessive amounts of purine and protein (for example, no more than 90 grams per day), dietary restrictions may be dispensed with.[72]

In more than 80 percent of patients with uric acid nephrolithiasis, increased fluid intake and alkalinization constitute sufficient therapy for control of further recurrences.[72,75] In some patients, partial and complete dissolution of existing stones was also observed. Fluid intake should be adequate to sustain a urine volume of least 1.5 to 2 liters per day. Therapy with sodium and potassium salts given orally is usually carried out to achieve a urine pH of 6.0 to 6.5. Insofar as is practicable, the urine flow and pH should be maintained as evenly as possible around the clock. Spot checks of urine pH with nitrazine paper may be done by the patient at home.

In patients who are either refractory to the above therapy or unsuitable for liberal hydration and alkalinization (for example, patients with precarious cardiovascular status), 200 to 400 mg of allopurinol per day may be administered in divided doses.[72] Allopurinol is rapidly oxidized to oxipurinol, which is also an effective xanthine oxidase inhibitor.[106] In contrast to the short half-life of allopurinol in plasma (1 to 1½ hours), that of oxipurinol is extremely long (18 to 30 hours). Some clinicians, therefore, prefer to give allopurinol in a single daily dose.[107] In patients with impaired renal function, a dosage of 100 mg of allopurinol per day may be adequate to maintain xanthine oxidase inhibition, because the clearance of oxipurinol is proportionately reduced. In a study of 108 patients refractory to conventional therapy, recurrence of renal colic and passage of uric acid stones discontinued in all except 10 patients soon after the institution of allopurinol therapy.[72]

Side effects of allopurinol include skin rash, drug fever, gastrointestinal irritation, thrombocytopena, impotence and granulocytopenia.[72,75] Skin rash resolves rapidly after withdrawal of allopurinol. Reinstitution of therapy in some of these patients was not followed by recurrence of the rash. With rare exceptions,[108,109] allopurinol administration did not cause overt problems with xanthine crystalluria and stones.[110] The inhibition of xanthine oxidase will retard the degradation of azathioprine and 6-mercaptopurine. In patients receiving these medications, the use of allopurinol should be avoided when possible. Otherwise, the dosage should be substantially reduced and toxicity from excessive immunosuppression closely monitored.

DR. KLEEMAN: *Acquired and congenital defects in the tubular reabsorption of various urinary solutes and the excretion of hydrogen ions result in a medullary intraluminal environment conducive to the precipitation and crystallization of various solutes. These, in turn, may lead to tubular degeneration and necrosis and, very frequently, nephrolithiasis. Dr. Robert Narins will report on these unusual patients.*

Renal Tubular Disorders Causing Nephrolithiasis

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THREE IMPORTANT DETERMINANTS of renal stone formation include (1) 24-hour urinary excretion of crystalloid, (2) its urinary concentration and (3) its solubility in the urine. These factors will be used as a framework for discussing the pathogenesis and therapy of nephrolithiasis in three renal tubular disorders: renal tubular acidosis, cystinuria and medullary sponge kidney.

Renal Tubular Acidosis

This syndrome may be subdivided into two major types whose pathogenesis and clinical expression differ substantially.[111] In proximal (type 2) renal tubular acidosis, bicarbonaturia occurs subsequent to the impairment of bicarbonate reabsorption by the proximal nephron. The defect in distal renal tubular acidosis (type 1) lies in the inability of the distal nephron to generate or sustain a urine of maximal acidity, despite severe systemic acidosis. In type 1, the daily load of endogenously produced acid is not excreted and a progressive systemic acidosis ensues. Unlike patients with distal renal tubular acidosis, who remain in positive acid balance, those with the proximal lesion are able to return to zero balance. The acidosis caused by their bicarbonaturia eventually lowers the filtered load of bicarbonate to an amount that can be again almost completely reclaimed by the damaged proximal nephron (Figure 6). At this point, bicarbonaturia will cease, and the urine may be again appropriately acidified and the daily load of fixed acid excreted. Thus, an inappropriately alkaline urine and positive hydrogen ion (H^+) balance characterize distal renal tubular acidosis, whereas patients with the proximal form excrete an acid urine and remain

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in zero H^+ balance, albeit at the expense of a lower serum bicarbonate concentration.

Nephrocalcinosis and nephrolithiasis frequently complicate distal renal tubular acidosis but rarely, if ever, occur in the proximal form. The prime determinant of calcium stone formation in distal renal tubular acidosis is a daily retention of acid. This results in hypercalciuria and leads to impairment of calcium's urinary solubility. The differences in calcium metabolism between types 1 and 2 of renal tubular acidosis, and the mechanisms of the hypercalciuria and calcium precipitation in the distal form of the disorder are discussed below.

The retained acid is partially buffered by bone calcium carbonate[112] causing release of calcium for excretion in the urine. The results of recent studies by Coe and Firpo[113] have shown that increased levels of circulating parathyroid hormone occur in distal renal tubular acidosis (type 1), thereby further enhancing the release of bone calcium. Consequently, bone density is frequently diminished in distal renal tubular acidosis (Table 3).

An increased concentration of circulating H^+ ions will reduce the negative charge on serum proteins. Thus, as more calcium circulates in the free form, more is available for glomerular filtration. The hypercalciuria that accompanies distal renal tubular acidosis is caused not only by this increased load of calcium, but also represents an acidosis-induced inhibition of tubular calcium reabsorption.[114] The mechanism by which acidosis depresses reabsorption is unknown at present, although it is probably due to an adaptation of the distal nephron to the acidosis.[115]

Bone disease rarely develops in patients with proximal renal tubular acidosis in the absence of phosphaturia, and, despite similar degrees of systemic acidosis, hypercalciuria is usually absent.[116] This is consistent with the minimal calciuric response of normal persons to acetazolamide-induced proximal bicarbonate wasting.[115] The absence of positive H^+ balance probably accounts for the lack of bone resorption and hypercalciuria in proximal renal tubular acidosis.

The persistently alkaline urine and hypocitraturia seen in distal renal tubular acidosis predispose to calcium crystallization. The hypocitraturia seems to be a reversible function of systemic and intracellular acidosis. Acidosis stimulates both citrate reabsorption and its metabolism by the

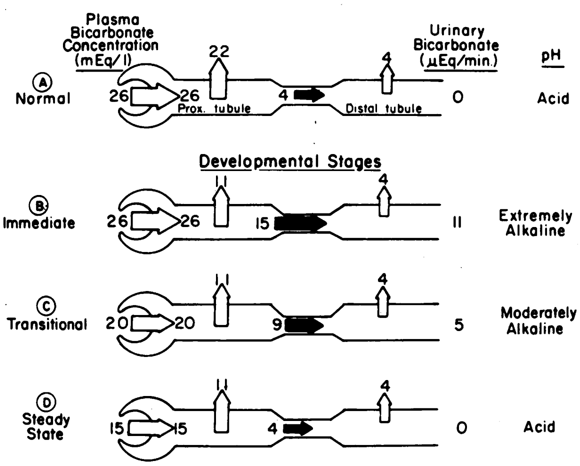


Figure 6.—Developmental stages of proximal renal tubular acidosis. Glomerular filtration, and proximal and distal reabsorption of bicarbonate designated by clear arrows. Dark arrow indicates the magnitude of the distal delivery of bicarbonate (see text for details). (Reproduced by permission from Narins and Goldberg[111]; copyright, 1977, by Year Book Medical Publishers, Inc., Chicago.)

TABLE 3.—*Pathogenesis of Nephrocalcinosis and Lithiasis in Distal Renal Tubular (Type 1) Acidosis*

Factors Causing Hypercalciuria	*Factors Enhancing Precipitation*
Bone	......
Bone buffering	
Parathyroid hormone	
Blood	......
Less protein binding	
Renal	Renal
Less tubular reabsorption of calcium	Alkaline urine
	Low urine citrate

TABLE 4.—*Therapy for Cystinuria*

Goal	*Procedure*
To enhance solubility	Alkalinization of urine (pH>7.5)
To reduce urinary cystine concentration	Water therapy of 3-4 liters per day
To reduce daily cystine excretion	A low protein diet and administration of penicillamine

TABLE 5.—*Comparison of Renal Cystic Diseases*

Feature	*Diseases* *MSK*	*MCD*	*PCK*
Clinical course	Benign	Fatal	Fatal
Renal stones	Common	Rare	Unusual
Hypercalciuria	Common	Common	Rare
Renal tubular acidosis	Occurs	Rare	Rare

MSK=medullary sponge kidney, MCD=medullary cystic disease, PCK=polycystic kidney disease epithelial cells of the renal tubules.[117] The resulting fall in citrate excretion leaves more urinary calcium in the noncomplexed form and, therefore, more prone to precipitation. The urine pH in proximal renal tubular acidosis, on the other hand, is not persistently alkaline and, therefore, hypocitraturia does not seem to occur. An associated defect in proximal citrate transport offsets any potential stimulation due to the accompanying acidosis.

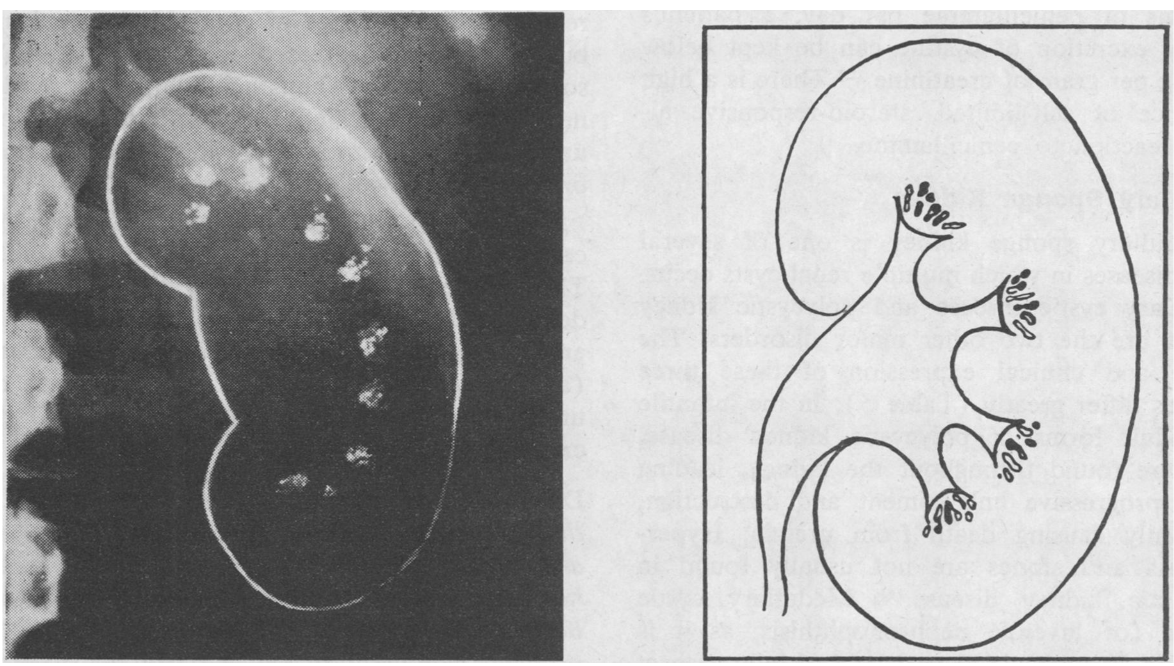
Thus, in distal renal tubular acidosis the renal delivery and excretion of calcium crystalloid is increased by its enhanced release from bone and its depressed tubular reabsorption. The high urine pH and low level of citrate excretion enhance precipitation. The absence of these features in proximal renal tubular acidosis explains the rarity of nephrocalcinosis and lithiasis in this form of the disease.

Alkali therapy reverses the effects of acidosis on bone and kidney, thereby returning the amounts of calcium and citrate excreted to within normal ranges.[118] With chronic therapy one may expect to see restoration of minerals to the bone and a diminution in preexisting nephrocalcinosis. Thus, therapy is directed toward diminishing the daily load of crystalloid and enhancing its solubility. Most patients require administration of between 80 and 100 mEq of alkali per day. This can easily be given as a mixture of sodium and potassium bicarbonate or as Shohl's solution (sodium and potassium citrate).

Cystinuria

The only recognized clinical expression of this disease is the urinary precipitation of the poorly soluble, sulfur-containing amino acid, cystine. This results in the formation of hexagonal (benzene-ring) crystals and eventually in radiopaque, staghorn calculi. Patients with cystinuria excrete large amounts of cystine, ornithine, arginine and lysine, despite normal plasma levels, indicating that defective tubular reabsorption and not excessive renal delivery causes the aminoaciduria. An intestinal defect in the absorption of these amino acids accompanies the renal lesion. The gastrointestinal lesion is clinically insignificant but serves as a very useful genetic marker. At present, the mechanism underlying this tubular and intestinal defect is not completely understood.[119]

The three major goals of therapy for cystinuria are outlined in Table 4. Although cystine solubility increases in alkaline urine, little benefit is



Medullary sponge kidney

MEDULLARY SPONGE KIDNEY WITH CALCIFICATION

Figure 7.—Medullary sponge kidney. Diagrammatic appearance of dilated papillary collecting ducts shown on right. Outline of the kidney on intravenous pyelogram is highlighted to emphasize the calcium stones in collecting ducts. (From Meschan[125]; reproduced by permission from WB Saunders Co.)

achieved from alkalinization until the urine pH exceeds 7.5.[120] The large dose of alkali required to achieve these pHs limits its usefulness. The intake of large quantities of water can reduce urinary cystine concentration below its saturation level of 300 mg per liter, thereby minimizing the chance of crystallization. Because many patients with cystinuria excrete 1 gram or more of cystine daily, they must drink 3 to 4 liters of water per day to achieve these low concentrations. They should awaken at night to take water and thereby prevent normal nocturnal oliguria. This is a safe and effective program that not only prevents stones from occurring but may dissolve those already present.[121] The degree of dietary protein restriction required to substantially lower cystine production and excretion is unacceptable to most patients and has little place in the routine therapy of cystinuria. Those patients who have lost substantial degrees of renal function or who have not responded to water therapy should be given penicillamine. Each molecule of cystine is composed of two molecules of cysteine, joined by a disulfide bond. Penicillamine disrupts this bond and binds cysteine, forming a mixed disulfide, which is more soluble than cystine and is excreted in the urine. With administration of 1 to 2 grams of penicillamine per day, a patient's urinary excretion of cystine can be kept below 200 mg per gram of creatinine.[122] There is a high incidence of self-limited, steroid-responsive allergic reaction to penicillamine.

Medullary Sponge Kidney

Medullary sponge kidney is one of several renal diseases in which multiple renal cysts occur. Medullary cystic disease and polycystic kidney disease are the two other major disorders. The course and clinical expression of these three diseases differ greatly (Table 5). In the infantile and adult forms of polycystic kidney disease, cysts are found throughout the kidney, leading to its progressive enlargement and destruction, eventually causing death from uremia. Hypercalciuria and stones are not usually found in polycystic kidney disease.[123] Medullary cystic disease (or juvenile nephronophthisis, as it is called in Europe) is caused by multiple cysts at the corticomedullary junction, which progressively replace renal tissue. The disease is associated with small kidneys and runs an inexorably downhill course to death in the second to third decade. These patients are often "salt-wasters," and also tend to excrete more calcium than their degree of renal failure otherwise warrants; yet nephrocalcinosis and nephrolithiasis are rare.[124]

Medullary sponge kidney is a benign disorder characterized by a variable degree of cystic dilatation of the papillary collecting ducts, which appear normal on x-ray films (Figure 7).[125] Small, discrete calcium-containing stones often develop in these dilated ducts and may serve as the first clue to the presence of sponge kidney. Because many of these patients remain asymptomatic, the diagnosis is not considered until a stone is passed, or until the renal calcifications are found serendipitously on an x-ray study of the abdomen.

Three factors may interact to cause these stones. First, the ectatic collecting ducts may lead to urinary stasis that may, in turn, predispose to calcium precipitation. Second, hypercalciuria and hypocitraturia seem to occur with increased frequency in this disorder.[126,127] Finally, in eight patients with medullary sponge kidney an associated renal tubular acidosis has been noted.[111] Four patients had overt signs of acidosis, whereas the defect could be recognized in the other four only by their failure to acidify maximally their urine in response to an acid load. The hypercalciuria in the study by Ekstrom[126] could not be related to the presence of renal tubular acidosis, but may reflect decreased collecting duct reabsorption of calcium. Thus, medullary sponge kidney is often associated with hypercalciuria, low urine citrate, inappropriately high urine pH and urine in dilated collecting ducts.

Once again, therapy is directed at lowering calcium excretion and enhancing its solubility. Those patients with associated renal tubular acidosis should be given alkali, which, in turn, may ameliorate the hypercalciuria and hypocitraturia (as mentioned previously). Chronic thiazide diuretic therapy has been used effectively to decrease the hypercalciuria seen in many patients.[127]

DR. KLEEMAN: *During past decades and up to the present, most of the fundamental laboratory and clinical investigation of renal stone disease has been done by urologists. Although efforts are being made to reduce and eliminate the need for urologic manipulation and surgical intervention, we still work very closely with our associates in urology and require their expertise and help. Dr. Richard Ehrlich of the Department of Surgery/Urology has frequently filled this role, and he will discuss the surgical aspects of renal calculi.*

Surgical Aspects of Renal Calculi

RICHARD M. EHRLICH, MD*

RENAL CALCULUS DISEASE continues to present a formidable surgical challenge. There is little, if any, disagreement about the necessity for surgical operations in symptomatic intrapelvic or calyceal calculi, which produce intermittent obstruction, infection, and hematuria or pain, or both. In these instances, the procedure is straightforward with emphasis placed on crystallographic analysis of stones, preoperative and postoperative control of infection and appropriate laboratory investigation for hyperparathyroidism.

The optimal management of the staghorn calculus, however, remains less clear. Some authors believe that nonoperative treatment is preferable in all asymptomatic patients and that renal function is not impaired by the presence of the calculus.[128] However, it has been our observation, and that of others,[129,130] that conservative treatment is complete operative removal. Swanson, Sullivan and Palmer[130] studied the cases of 30 patients with branched renal calculi in whom operative removal was carried out by various procedures. Of the patients, 83 percent were rendered free of stones and 80 percent free of infection, with no operative mortality. Furthermore, in this series renal function improved or stabilized in patients who had impairment of function before the operation.

Blandy and Singh[129] reported a 28 percent mortality among 60 patients with staghorn calculi; in 40 patients treated conservatively, pyonephrosis and other complications ensued. They concluded that all staghorn calculi should be removed, with which we agree, if preoperative evaluation of a patient's medical condition permits.

Several advances in surgical technique have made this approach valid. The parenchymal-sparing renal sinus approach of Gil-Vernet[131] and anatrophic nephrolithotomy of Smith and Boyce[132] are now used by most urologists. The latter is particularly well suited for complex, branched stones filling the entire calyceal system, and is predicated on precise vascular anatomic studies. After careful preoperative radiographic studies in multiple projections (and, occasionally, arteriography), a renal incision is made between separately supplied renal segments to spare the maximum number of nephrons. This incision is based on the anatomic fact that intrarenal arteries are "end arteries" and do not freely anastomose between segments as does the venous system. Using in vivo hypothermia (7° to 20°C) provided by iced saline slush, the ischemic period may be extended to more than two hours, which allows for enough time to insure complete stone fragment removal.[133]

The other surgical procedures, such as pyelocalycotomy[134] and lower pole partial nephrectomy,[135] are helpful in special conditions to prevent stone recurrence, but do result in some renal parenchymal loss. No one operative approach is applicable to all situations, and thorough familiarity with the above is mandatory for urologic surgeons.

Successful surgical operations to remove stones is predicated on meticulous attention to metabolic, bacteriologic and renal function evaluation, and implies complete removal of all stone fragments and correction of anatomic deformities. For an excellent in-depth analysis of the important facets of this type of procedure, we recommend the report of the Symposium on Renal Lithiasis.[136]

The ileal ureter deserves special mention. At the UCLA Hospital a total of 44 patients have been treated with ileal substitution for multiple recurrent renal calculi refractory to traditional forms of therapy. This procedure, although surgically demanding, is excellent in patients with severe nephrocalcinosis and a history of passing multiple stones. The principle of the procedure is to provide maximum drainage of the renal pelvis and lower calyces. This is to prevent recurrence of stones and to allow free passage of stones already formed into the bladder where they will be voided easily or removed cystoscopically. Contraindications to the procedure are small bowel disease, serum creatinine (higher that 2 mg per dl), neurogenic bladder or outlet obstruction.[137,138]

Most surgical failures and recurrence of stones are related to incomplete removal of fragments of the original stones. Operative nephroscopy, copious irrigation and intraoperative radiography are mandatory surgical aids to insure that even the smallest fragments are removed. If this is not successful, continued infection with urea-splitting organisms is likely. A concomitant de-

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creased solubility of both struvite and calcium salts in the resultant alkaline medium assures reformation of stones.

A recent resurgence of interest in coagulum pyelolithotomy (the formation of an intrapelvic clot with fibrinogen and thrombin) deserves special mention and has been used with outstanding success in removing small intrapelvic fragments and tiny stones. Fibrogen and thrombin are injected into the renal pelvis simultaneously, the coagulum enmeshing stone fragments. The clot is then removed with the entrapped material. Its use has not received the attention it warrants, but will probably be more widely employed in the future.[138-142]

Another indispensable aid for postoperative stone dissolution in those instances where it is impossible to free the kidney of fragments intraoperatively is the use of hemiacidrin (Renacidin, Guardian Chemical Corporation, Long Island, NY 11787)[143-145] in renal irrigation via indwelling nephrostomy. It is safe and effective but must be used with appropriate clinical safeguards, particularly the assurance of sterile urine.

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Myasthenia Secondary to Penicillamine

MYASTHENIA HAS BEEN FOUND to be a complication of penicillamine, a drug being used increasingly in the treatment of rheumatoid arthritis. . . . After years of speculation about a possible chemical abnormality as the cause of myasthenia, recent work has pinpointed the defect to a decreased number of available acetylcholine receptors in muscle. The decrease in the number of available receptors is due to the binding of many of these receptors by antiacetylcholine receptor antibodies. . . . Since penicillamine is known to produce some of its complications by means of antibody induction, and since myasthenia is now felt to be caused by antiacetylcholine receptor antibodies, which block uptake of the neural impulse at the neuromuscular junction, one can speculate that penicillamine may induce antibody to acetylcholine receptors and thereby cause myasthenia in susceptible patients. So far, more than 30 cases of penicillamine-induced myasthenia have been reported, and almost all of the cases have resolved simply by withdrawing the drug. . . . Treatment with standard antimyasthenia therapy is usually unnecessary.

—PAUL E. PATAKY, MD, *Boston*

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